Claims 18, 21, 26, 33, 35-36, 41, 68-71, 73-78 and 80-82 remain pending in the application. Claims 19-20, 22-25, 34 and 38-40, 72 and 79 have been canceled, and Claims 74 and 81 are amended to put the application into better form for appeal.

Information Disclosure Statement

Applicants submit herewith two substitute disclosure statements, one a Supplemental Information Disclosure Statement in the 1449 format. All references to related applications have been deleted from the 1449 IDS and placed in a second information disclosure statement. Copies of references cited in latter filed related applications are submitted in the second statement.

Benefit of Priority Dates

Applicants note the comments in their last response with regard to filing dates.

Objections to the Specification and Rejection of the Claims

Please consider the following remarks in regard to the objections made to the specification and specific rejections made in the Office Action.

35 U.S.C. § 112, Second Paragraph

Claims 18, 21, 26, 33, 35-36, 41, 68-71, 73-78 and 80-82 are rejected by the Patent Office as being indefinite for

failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Office Action alleges that claims directed to the modification of total fatty acids are redundant to claims directed to modification of the fatty acid compositions of oil triglycerides, stating further that Applicants' specification fails to make such a distinction. The Examiner specifically contends that Claims 18, 21-22, and 26 duplicate Claims 33, 36 and 41, and likewise that claims 68-72 duplicate claims 76-79 while Claims 73-75 duplicate Claims 80-82. Applicants respectfully traverse these rejections and request reconsideration.

The specification as filed included claims to both types of modification. For this reason alone the rejections under this provision are in error, in stating that the Application does not make such a distinction. It is well established that the claims as filed form a part of the original disclosure of the Application.

Furthermore, under § 112, second paragraph, an applicant is required to claim that subject matter which he or she regards as the invention. For purposes of this provision the subject matter set forth in the claim is that which is regarded as the applicant's invention, in the absence of evidence to the contrary. Thus, the only proper rejection of a claim for failure to claim the subject matter regarded as the invention is would be in a situation where some evidence, other than the specification, suggests that a claim does not

correspond in scope with what the inventor regards as the invention. The fact remains that there is a distinction in modifying the fatty acid pools and the triglyceride fatty acid compositions in oil cells. As Applicants regard this as part of their invention, Applicants are permitted to claim their invention as such.

Finally, Applicants again note that the original restriction in this case identified claims directed to the modification of triglyceride acyl fatty acids as comprising a patentably distinct species (group (c)) with respect to the generic Claims 18, 21 and 26, designated Group II. Applicants noted previously and again submit that the present rejection is inconsistent with the previous status position taken by the office. The restriction requirement clearly identified Claims 18, 21 and 26 as generic to the "patentably distinct species comprising" the triglyceride acyl fatty acid claims, namely Claims 22 and 33-41. On this basis Applicants made their election, in a November 5, 1992 response, to prosecute group II and subspecies (c) as the elected invention.

Claims 22 and 72 are canceled, obviating that part of the rejection specifically directed to those claims.

In view of the above, Applicants respectfully request that the 35 U.S.C. § 112, second paragraph rejections of the claims be withdrawn.

35 U.S.C. § 112, Second Paragraph

Claims 79 is canceled by amendment herein, while Claims 74 and 81 have been amended to omit the term "homologous". It is believed that these amendments obviate the rejection under the above provision with respect to those claims.

35 U.S.C. § 112, First and Second Paragraphs

Claims 18, 21, 26, 33, 35-36, 41, 68-71, 73-78 and 80-82 are rejected under the above provisions for non-enablement and for failure to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Applicants respectfully traverse these rejections, and request reconsideration.

Applicants again note that the constructs disclosed in the specification are intended to be exemplary and are not necessary to practice the invention as claimed. The specification describes the development of various sense and antisense constructs in great detail, including all restriction sites and their locations. Even were the precise constructs necessary to practice the invention, one ordinarily skilled in the art would require nothing more than the disclosure in the specification to make or reproduce the invention.

However, the precise constructs are not necessary to practice the claimed invention. The state of knowledge of those ordinarily skilled in the art at the time of the invention was such as to permit the production and use of such a construct given nothing more than the desaturase

sequence, without undue experimentation. This much is apparently conceded in the Office Action, in the discussion of the Shewmaker *et al.* reference cited against the claims under §103. Applicants note the characterization of Shewmaker *et al.* in the Office Action dated September 21, 1993, as teaching "the application of antisenese for any gene in order to reduce expression of the message encoding the product of that gene" (page 7).

In fact, at the time of invention the state of the art included successes in modifying a number of basic biochemical processes in plants, including fruit ripening. (Shewmaker *et al.*), flower color (anti-sense chalcone synthase; van der Krol *et al.*) and a photosynthetic enzyme (anti-sense of RuBisCo subunit (Rodermel *et al.*). Copies of each of these references have been introduced into the file history during prosecution.

Applicants have provided the necessary desaturase sequence, successful examples using both orientations and both endogenous and exogenous cDNA, and have additionally disclosed specific information regarding both specific and general promoters. So long as a person skilled in the art can make and use an invention without undue experimentation, combining the knowledge of the prior art with the disclosure of the specification, nothing more is necessary to enable the invention.

There is no reason or evidence of record in the application which would indicate that the desaturase enzyme

is somehow more unpredictable and thus not similarly amenable to anti-sense inhibition. It is well established that Applicants are not required to teach in the specification what is already well known to the skilled artisan. Given this extent of knowledge of anti-sense methods for plant phenotype modification in the art, the knowledge of transcriptional initiation regions useful in plant cells, methods for the transformation of plant cells and methods to measure desaturase levels and/or activity, all the information that one skilled in the art really needed to achieve anti-sense inhibition is the claimed constructs.

The above arguments are believed to overcome the rejection under §112 first and second paragraphs, and withdrawal is respectfully requested.

35 U.S.C. § 112, First Paragraph

The Patent Office has objected to the specification and rejected Claims 18, 21, 26, 33, 35-36, 41, 68-71, 73-78 and 80-82 as not enabling the practice of the claimed invention.

Applicants invention, as described in the specification and as reflected in the claims under consideration, involves the use of a recombinant DNA construct which is integrated into the genome of a plant host cell. This construct encodes a fatty acid modifying plant desaturase sequence under the control of regulatory elements functional in the plant cell. Applicants have claimed, and the specification supports, antisense inhibition as but one approach which can be taken

to modify fatty acid composition. It is not an invitation to experiment to state that the disclosure of the specification is so complete that one ordinarily skilled in the art could use it in modifying the invention with alternate sequences or sequences from other sources. It is, rather, an indication of the completeness and extent of the description contained in the specification, in that only routine experimentation is required.

Applicants have clearly enabled both sense and antisense constructs, and for this reason respectfully request that the §112, first paragraph objection to the specification and rejection of the claims be withdrawn.

Applicants note as an aside that construct pCGN3242 was been deposited under a depository accepted under the Budapest Treaty for patent deposits. This deposit was not made in accordance with the prosecution of the instant application, as Applicants contend that the description of the invention is complete and detailed and sufficient for one ordinarily skilled in the art to duplicate the invention absent such a deposit.

The deposit was a DH5 alpha *E. coli* strain containing the binary vector with antisense desaturase in an ACP cassette and napin cassette, identified as plasmid pCGN3242. This deposit was made with the American Type Culture Collection (ATCC), an International Depository Authority under the Budapest Treaty. The specific strain will be

irrevocably and without restriction or condition released to the public upon the issuance of a patent.

Specifically, the deposit was made as an ATCC Patent Deposit on December 3, 1993. It was given an ATCC No. of 69506. The accession number for the deposit is 4125. The address for the ATCC is as follows:

12301 Parklawn Drive
Rockville, Maryland 20852-1776

Applicants reiterate that this deposit, and the information provided herein, is not believed to be necessary to obviate this rejection, and is not submitted as an admission or acquiescence on the merits of this rejection. (See *Quad Environmental Technologies Corp. v. Union Sanitary District*, 20 USPQ 1392 (Fed. Cir. 1991)).

35 U.S.C. § 112, First Paragraph

Applicants traverse the rejection of Claims 18, 21, 26, 33, 35-36, 41, 68-69, 71, 73-74, 76-77 and 80-81 were rejected under the above provision as overly broad. In any event, Claims 70, 75, 78 and 82 contain the limitations mentioned by the Examiner, and were not rejected under this provision.

Enabling only for Transformation using Antisense Orientation

On pages 110-113 the results of measurements made on the total fatty acid compositions of selected mature seeds are given. On page 86, the results of measurements of fatty acid

contents are shown for plants resulting from an experiment wherein a single napin promoter construct was used in transformation, the construct including a single copy of a sense-oriented desaturase cDNA. For each example, changes in at least two fatty acid levels are disclosed.

Thus, the Examiner is simply wrong in stating that only antisense inhibition has been enabled.

Enabling only for Transformation with DNA from *Brassica*

Contrary to the suggestion in the Office Action, Example 9 clearly discloses that modification using safflower stearoyl-ACP encoding sequences were made in *Brassica*, and exactly what those modifications were. These are not hoped for results, and neither are the results describing the results of antisense experiments. Applicants' have disclosed modification of fatty acid and oil triglycerides in *Brassica* using both *Brassica* and non-*Brassica* cDNA encoding the desaturase protein. They are not, then, limited to claiming *Brassica* cDNA for the methods of modification.

The Examiner also states that expressing an encoded protein is not the same as inhibiting expression. However, Applicants' claims are not limited to antisense expression, so the Example 9 embodiment is relevant to the rejections of those claims which do not recite an antisense limitation.

Enabling only for Transformation with Stearoyl-ACP Desaturase

Claims 68-69, 71, 73-74, 76-77 and 80-81 recite methods of modifying the fatty acid composition of a plant host cell which specifically recite a construct encoding a plant stearoyl-ACP desaturase.

Applicants have previously noted that the remaining claims rejected under this provision, while covering other than stearoyl-ACP desaturases, such as those named at page 4, are enabled as the instant specification provides a first successful demonstration of a means for modifying plant saturated fatty acid compositions using a recombinant construct. It is reasonable to extrapolate from these results that alternative desaturases may be used successfully in the modification of fatty acid levels. While plant fatty acid enzymatic pathways are complicated, desaturase enzymes are not known to be a rate-limiting or particularly critical reaction of these pathways. Applicants are the first to demonstrate, as a principal, that if an exogenous fatty acid biosynthesis enzyme is introduced, or an endogenous enzyme inhibited by expression of a fatty acid enzyme from a recombinant construct, that a modification of total saturated fatty acid levels will result.

In view of the above, Applicants submit that they are entitled to methods as recited in Claims 18, 21, 26, 33, 35-36, 41, 68-69, 71, 73-74, 76-77 and 80-81, using plant desaturase encoding constructs to modify cell fatty acid

compositions, and respectfully request that the 35 U.S.C. §112, first paragraph rejection to the claims be withdrawn.

35 U.S.C. § 103

Claims 18, 21, 26, 33, 35-36, 41, 68-71, 73-78 and 80-82 are rejected as unpatentable over Kridl *et al.* taken with Knauf and Shewmaker *et al.*, and further in view of McKeon *et al.* and Weissman *et al.* This rejection is respectfully traversed as follows.

Weissman *et al.*

In the Office Action, this reference is characterized as teaching that all one of ordinary skill in the art needed in order to obtain cDNA for any gene was a purified protein preparation. As Applicants have noted, the Federal Circuit has reviewed the teachings of the *Weissman et al.* reference (*In re Bell*, 26 USPQ2d 1529 (Fed. Cir., 1993)). The issue of *In re Bell* was whether "the amino acid sequence of a protein in conjunction with a reference indicating a general method for cloning renders the gene *prima facie* obvious." *In re Bell* at 1531. The Patent and Trademark Office had argued that "in view of Weissman, a gene is rendered obvious once the amino acid sequence of its translated protein is known." *Id.* at 1532.

The Federal Circuit held in that case that a rejection of an invention based on Weissman *et al.* and a primary reference showing the amino acid sequence "amounts to a

rejection based on the" sequence of the primary reference alone. *Id.* at 1531.

Under the Federal Circuit's reasoning in *In re Bell*, the Weissman *et al.* teaching simply could not render the nucleic acid sequence of such a purified protein obvious. Nevertheless, in the Office Action it is stated that at the time of Applicants invention the teachings of Weissman *et al.* were sufficient to render the nucleic acid sequence to a partially purified protein obvious. The Weissman *et al.* reference did not change during this time, and so presumably it was the state of the prior art which changed to such a degree that the holding of *In re Bell* became irrelevant, yet no evidence of record is cited as suggesting that Weissman *et al.* had a greater or different significance to the skilled worker in the art at the time of Applicants' invention than at the time of the invention under consideration in *In re Bell*.

Applicants note particularly the Federal Circuit's express holding that the claimed nucleic acid sequence would not have been obvious because an amino acid sequence is only a suggestion of the vast number of possible DNA sequences which could encode for that amino acid sequence. *Id.* at 1531.

While the instant application was filed several years after the application was filed in *In re Bell*, based on the present fact situation the desaturase DNA is even less obvious than was the situation for the DNA in *In re Bell*. In

In re Bell the primary reference provided the amino acid sequence for the protein, while McKeon *et al.* does not provide an amino acid sequence for the desaturase protein, but only purports to disclose a purified desaturase protein preparation. Given the above, it is clear that the combination of Weissman *et al.* and a purified protein preparation would not render obvious the cDNA to that protein.

Additionally, both of the claims currently under consideration specifying a *Brassica* desaturase encoding sequence, while the secondary reference, McKeon *et al*, purports to provide a purified desaturase protein preparation from *Carthamus tinctorius*. No reference provides a partial amino acid or nucleic acid sequence to a desaturase from that or any other source.

In any case, and as argued below in greater detail, while McKeon *et al.* claims to provide a method to obtain a highly purified desaturase protein, Applicants have demonstrated that the protein obtained by this method is, in fact, highly contaminated, and thus not suitable for the amino acid sequencing method discussed in Weissman *et al.*.

McKeon *et al.*

McKeon *et al.* is cited as providing a purified protein preparation of a stearoyl-ACP desaturase from safflower. Applicants have demonstrated that the McKeon *et al.* preparation is not purified. To be prior art a reference

should put the anticipating subject matter at issue into the possession of the public through an enabling disclosure. In the course of prosecution of this case, Applicants have submitted a copy of a declaration of Dr. Gregory Thompson, highlighting problems that Applicants encountered in attempting to duplicate the McKeon *et al.* purification.

In his declaration Dr. Thompson elaborates on the difficulty in obtaining a purified desaturase protein preparation, which difficulty is also recounted in the specification (*see*, specification, page 24, lines 10-19; also Examples 2 and 3). The problems with the McKeon *et al.* preparation led the inventors to initially clone a cDNA for albumin, after hybridization with oligonucleotides derived from what was believed to be an amino acid sequence from a purified desaturase. Only after Applicants applied HPLC analysis techniques to the desaturase preparation did they discover the albumin contamination of the preparation. Analysis by an even more precise method, the amino acid technique, determined that albumin, not desaturase, was the major component, on a mole percentage basis, of the "purified" preparation of safflower desaturase obtained by following the method of McKeon *et al.*.

With respect to this declaration, the Examiner notes that the band which is on the sizing gel shown in McKeon *et al.* appears to be homogenous. Obviousness cannot be established, however, by combining the teachings of the prior art to produce the claimed invention when there is no

teaching or suggestion supporting the combination. Here the Examiner has taken the fact of a contaminant which is reported only in Applicants specification, and used this as the motivation to combine a further purification step which was known to those skilled in the art, but which is not suggested or taught in the prior art for this invention.

The albumins contaminating the protein prepared according to the method of McKeon *et al.* have been determined by Applicants to have a molecular weight range of about 10 to about 18 kilodaltons. Based on this estimation, the contamination would not have been visualized in the gel shown in Fig. 2 of the McKeon *et al.* paper, as the small molecules would have run to a position off the top end of the gel depicted in that figure (note molecular weight markers in left margin of figure). In Applicants' hands gels run on the contaminated protein preparation similarly appeared to show a single predominant protein band, falsely suggesting a homogeneous preparation, or at least a very high level of purification for the protein. Thus, no further purification was deemed necessary.

Any suggestion that the McKeon *et al.* preparation was at least pure enough to allow one to further experiment and cut out a band of desaturase from a gel presumes that the contamination was known, while it is clear from the record that this protein <u>was already believed to be pure</u>. For this reason it would <u>not</u> have been obvious, but rather would have <u>seemed a waste of time</u>, for one to apply a further

purification step to the procedure of McKeon *et al.*.

Thus, even if the "band" of McKeon *et al.* is "pure" in a sense, though imbedded in a polymeric gel matrix, the suggestion to cut out this band is a classic example of hindsight recreation of an invention. The polyacrylimide gel in McKeon *et al.* was not used in a preparatory context for the purification of the protein, but merely as means for verification of what had presumably gone before, the complete purification of desaturase, and for estimation of the size. It is only in hindsight, having the benefit of Applicant's specification in one hand, and viewing McKeon *et al.* in the other, does it become clear that a further purification of reductase is necessary.

The Primary and Secondary References

Viewing the various primary and secondary references as a whole or in combination, they do not teach or suggest Applicants' invention as recited in Claims 68 and 75, nor do they render the same obvious.

Kridl *et al.*

The primary reference, Kridl *et al.*, discloses seed specific expression of an ACP gene during lipid development. There is no disclosure in the Kridl *et al.* reference of a recombinant plant desaturase-containing cDNA construct. Kridl does not teach or suggest a stearoyl-ACP desaturase, let alone a stearoyl-ACP desaturase-encoding DNA.

Knauf

The Knauf secondary reference, while directed to the genetic engineering of plants, does not teach or suggest a stearoyl-ACP desaturase sequence. While Knauf discusses potential targets for research, such as increasing oil production and altering fatty acid compositions, there is no suggestion of a specific cDNA or a suggestion of the composition of a construct for any purpose. Thus, while Knauf may have provided a motivation to attempt to prepare constructs to introduce fatty acid synthase pathway genes into plants, such an attempt remained impossible without specific encoding sequences to fatty acid synthase pathway genes, such as the desaturase sequence provided by this invention.

Shewmaker *et al.*

Shewmaker *et al.* teaches the use of an anti-sense cDNA construct for regulation of a plant gene. The gene in question is not a fatty acid synthesis gene, and Shewmaker *et al.* does not provide the sequence to the desaturase cDNA of the invention.

These primary and secondary references may provide a motivation for further research or inquiry in the area of fatty acid synthesis genes. Their teachings do not provide the element of a desaturase sequence which is absent in the tertiary references, nor do they teach anything which, when

combined with the tertiary references, would render the invention obvious.

As the claimed invention is only possible given the unique cDNA to plant desaturase provided by Applicants in their specification, which cDNA is neither taught nor suggested in any disclosure of the prior art, Applicants respectfully request withdrawal of the 35 U.S.C. §103 rejection of the claims.

CONCLUSION

In view of the above, Applicants submit that the instant application is in immediate condition for allowance and early notice to this effect is solicited. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the application, the Examiner is invited to contact the undersigned at (916)753-6313.

Respectfully submitted,

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Enclosure: Notice of Appeal